Remarks

A Request for Continued Examination is made in this Reply to the Office Action dated March 21, 2007. Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-5, 7-13, 15-17 and 19-22 are pending in the application, with claims 1 and 21 being the independent claims. These changes are believed to introduce no new matter, and their entry is respectfully requested.

The amendments to claims 1 and 19 and the addition of claims 21 and 22 are intended to clarify the present invention and to put the claims in condition for allowance.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

I. Rejections Under 35 U.S.C. § 112, First Paragraph

A. Written Description / New Matter

The Examiner has rejected claims 1-5, 7-13, 15-17, 19 and 20 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement (new matter). The Examiner asserts that there is no support for

> culture media that consist of DMEM (Dulbecco's modified Eagle's medium), F12 medium, insulin and one or more additives selected from the group consisting of NaHCO3, sugars, ethanolamine, pyruvate, amino acids and mixtures thereof.

(OA at page 3.) Applicants respectfully traverse this rejection.

To fulfill the written description requirement of 35 U.S.C. § 112, first paragraph, a patent specification must describe an invention in sufficient detail that one skilled in the art can clearly conclude that the inventors invented the claimed subject matter. *See Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1566, 43 U.S.P.Q.2d 1398, 1404 (Fed. Cir. 1997). Stated differently, the written description requirement is satisfied when the specification "set[s] forth enough detail to allow a person of ordinary skill in the art to understand what is claimed and to recognize that the inventor invented what is claimed." *University of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 928, 69 U.S.P.Q.2d 1886, 1896 (Fed. Cir. 2004). Moreover, an important consideration in assessing written description of a claimed invention is the knowledge of one skilled in the art. *See Bilstad v. Wakalopulos*, 386 F.3d 1116, 1126, 72 U.S.P.Q.2d 1785, 1792 (Fed. Cir. 2004).

According to the Federal Circuit, "[i]t is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention." *Capon v. Eshhar*, 418 F.3d 1349, 1359, 76 U.S.P.Q.2d 1078, 1085 (Fed. Cir. 2005). In addition, when generic elements of a claim are so well known and thoroughly characterized in the art that their recitation alone is sufficient to convey distinguishing information regarding their identity, the written description requirement for those elements is fully satisfied. *See Amgen Inc. v. Hoechst Marion Roussel Inc.*, 314 F.3d 1313, 1332, 65 U.S.P.Q.2d 1385, 1398 (Fed. Cir. 2003).

Finally, a description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the Examiner to

rebut the presumption. *See, e.g., In re Marzocchi*, 439 F.2d 220, 224, 169 U.S.P.Q. 367, 370 (CCPA 1971). The Examiner, therefore, in making a rejection must have a reasonable basis to challenge the adequacy of the written description. The Examiner has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an Applicant's disclosure a description of the invention defined by the claims. *See In re Wertheim*, 541 F.2d 257, 263, 191 U.S.P.Q. 90, 97 (CCPA 1976).

The specification as-filed provides adequate written descriptive support under 35 U.S.C. §112, first paragraph, for a "culture medium consisting of DMEM (Dulbecco's modified Eagle's medium), F12 medium, insulin, $NaHCO_3$, sugars, ethanolamine, pyruvate, and amino acids" as currently claimed. More specifically, originally filed claims 1 and 6 were drawn to a method for obtaining human erythropoietin (hereinafter "EPO") comprising culturing mammalian cells which express recombinant EPO in culture medium comprising insulin (claim 1) and wherein the culture medium is fetal-calf serum free (claim 6). The originally filed claims are broadly drawn to fetal-calf serum free (hereinafter "SF") culture media comprising insulin, while the culture media disclosed on page 14 of the present specification comprises DMEM, F12 and insulin as well as additives. The as-filed claims and the description on page 14 of the specification provide descriptive support covering a range of SF culture media. This information in conjunction with what was known in the art provide adequate descriptive support for the invention as now claimed.

In particular, the specification and claims as-filed provide proper written descriptive support for SF culture media with additives, specifically "$NaHCO_3$, sugars,

ethanolamine, pyruvate, and amino acids." The predecessor to the Court of Appeals for the Federal Circuit held that the inventor need not describe in his specification the full range of equivalents of his invention. *See In re Noll*, 545 F.2d 141, 149-50 (CCPA 1976); cf. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986) ("a patent need not teach, and preferably omits, what is well known in the art"). Furthermore, written description does not require that the subject matter of the claim need be described literally, i.e., using the same terms or *in haec verba*, in order for the disclosure to satisfy the description requirement. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even though it is not explicitly described in the specification, then the adequate description requirement is met. *See, e.g., Vas-Cath, Inc. v Mahurkar*, 935 F.2d 1555 at 1563 (Fed. Cir. 1991); *Martin v. Johnson*, 454 F.2d 746, 751, 172 USPQ 391, 395 (CCPA 1972) (stating "the description need not be in *ipsis verbis* [i.e., "in the same words"] to be sufficient"); *see also* MPEP §2163.

There is descriptive support for the term "sugars" in the specification. Culture Medium No. 3 (*see* specification page 14) discloses the supplementation of sugars and amino acids in the basal medium supplemented with insulin. Specifically, the specification discloses the use of DMEM and Ham's F12 medium, and both media contain the sugar glucose in their formulation. **(Exhibits A and B.)** Furthermore, culture Medium No. 3 discloses the additional sugars lactose and galactose. Thus, the specification provides descriptive support for the term "sugars" as used in the presently amended claims.

There is likewise descriptive support for the term "amino acids" in the specification. Culture Medium No. 3 (*see* specification page 14) discloses the supplementation of amino acids in the basal medium supplemented with insulin. Specifically, the specification discloses the use of DMEM and F12 medium; both media contain the following amino acids in their formulation: alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine and valine. **(Exhibits A and B.)** Accordingly, all 20 naturally occurring amino acids are present in the media disclosed in the specification. Furthermore, Medium No. 3 (*see* specification page 14) additionally adds tryptophan, asparagine, serine and glutamine to the SF medium. Thus, the specification provides descriptive support for the term "amino acids" as used in the presently amended claims.

The Examiner has the initial burden of establishing a reasonable basis for challenging the adequacy of the written description for a claimed invention. *See Wertheim*, 541 F.2d at 263, 191 U.S.P.Q. at 97. In view of the conclusory arguments presented by the Examiner that are unsupported by the evidence of record and the current state of the law regarding written description, Applicants assert the Examiner's burden has not been met.

In summary, claims 1-5, 7-13, 15-17 and 19-22 are adequately described by the specification as one skilled in the art would clearly conclude that Applicants invented the claimed subject matter. Therefore, Applicants respectfully request reconsideration and withdrawal of the present rejection.

B. Enablement

The Examiner has rejected claims 1-5, 7-13, 15-17, 19 and 20 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. More specifically, the Examiner asserts that "[t]he specification fails to disclose growth and proliferation of recombinant CHO, COS, BHK, Namalwa and HeLa cells for the production of rEPO in serum free culture media (as claimed)." (OA at page 4.) The Examiner alleges that

> [t]he scope of culture medium as claimed (for example) is limited to DMEM, F12, insulin and NaHCO3, which render the use of such medium highly unpredictable as it is well established in the tissue culture art that cell[s] require[ ] glucose and amino acids to proliferate and produce recombinant proteins.

(OA at page 5.) Applicants respectfully traverse this rejection, and request that the Examiner reconsider and withdraw the rejection in view of the remarks below.

1. Breadth of the Claims and Guidance Provided in the Specification

The Examiner alleges that "[t]he claim(s) contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention." (OA at page 4.) Specifically, the Examiner asserts that the use of culture medium limited to DMEM, F12, insulin and NaHCO3 is highly unpredictable because the production of recombinant proteins requires that glucose and amino acids must be present in the medium. In essence, the Examiner asserts that the claimed culture medium does not contain glucose and amino acids and that culture medium limited to DMEM, F12, insulin

and $NaHCO_3$ likewise does not contain glucose and amino acids. Applicants respectfully disagree on both accounts.

"As concerns the breadth of a claim relevant to enablement, the only relevant concern should be whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims." MPEP § 2164.08 (2006) (citing *AK Steel Corp. v. Sollac*, 344 F.3d 1234, 1244 (Fed. Cir. 2003); *In re Moore*, 439 F.2d 1232, 1236 (C.C.P.A. 1971); *see also Plant Genetic Sys., N.V. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1339 (Fed. Cir. 2003).

It is well known to the ordinary artisan that DMEM and F12 medium comprise both glucose and amino acids. **(Exhibits A and B.)** Thus, even if the medium were limited to only DMEM, F12, insulin and $NaHCO_3$, the medium would work for the production of recombinant proteins because the medium contains glucose and amino acids.

Further, the presently-pending claims are directed to a method of producing EPO by culturing the cells in "culture medium consisting of DMEM (Dulbecco's modified Eagle's medium), F12 medium, insulin, $NaHCO_3$, **sugars**, ethanolamine, pyruvate, and **amino acids**." Example 1 of the present specification discloses the use CHO cells transfected with genomic DNA of human EPO, the expansion of the cells (Examples 2-5), and the incubation with SF media (page 14 of the present specification). Accordingly, the present specification provides at least one working example that falls within the scope of the presently pending claims. Further, Wang *et al.*, Yang. *et al.*, Schroder *et al.* and Lee *et al.*, art cited by the Examiner, provide teachings that there are

many different SF cell culture media formulations that allow for the production of recombinant proteins in cell culture. As such, Applicants assert that specification as-filed provides an enabling disclosure consistent with the full scope of the presently-pending claims.

2. State of Art and Predictability

The Examiner alleges that

> [i]n [the] instant case large scale industrial production of rEPO in serum free conditions (as claimed) is not considered routine in the art and without sufficient guidance to the host cells, contents and concentrations in the culture media used the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

(OA at page 8.) Applicants respectfully disagree.

Applicants have demonstrated that the invention produces EPO in SF culture medium as claimed. The Examiner has not provided specific evidence to the contrary; therefore, there is no reason to doubt Applicants' assertion that the claimed method will obtain EPO from a "culture medium consisting of DMEM (Dulbecco's modified Eagle's medium), F12 medium, insulin, $NaHCO_3$, sugars, ethanolamine, pyruvate, and amino acids." *See In re Marzocchi*, 439 F.2d 220, 224 (C.C.P.A. 1971) ("[I]t is incumbent upon the Patent Office . . . to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement."); *see also In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993). The specification in Examples 6-8 provides a method of culturing the mammalian cells, specifically CHO, under conditions that use SF medium and contain insulin for the production of EPO. Furthermore, the EPO

obtained by the present method contains the complex carbohydrate structures and the sialic acid terminal residues (*see* specification page 12, lines 1-6). Thus, the present specification has enabled the production of EPO in SF cell culture medium as claimed.

The Examiner also alleges that "[s]everal culture parameters could affect the metabolism of cultured cells and hence affect the glycosylation and sialylation of secreted glycoproteins. These factors include combination of nutrition, concentration and accumulation of by products." (OA at page 5.) The Examiner cites several references, Wang *et al.*, Yang. *et al.*, Schroder *et al.* and Lee *et al.*, for the proposition that there is unpredictability in the art.

The MPEP provides guidance with respect to the enablement requirement, stating that "[a]s long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied." § 2164.01(b) (citing *In re Fisher*, 427 F.2d 833, 839 (CCPA 1970)). Additionally, "a specification disclosure which contains a teaching of the manner and process of making and using the invention . . . . must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied upon for enabling support." *Rasmusson v. Smithkline Beecham Corp.*, 413 F.3d 1318, 1323 (Fed. Cir. 2005) (quoting *In re Marzocchi*, 439 F.2d 220, 223 (C.C.P.A. 1971)).

The application as-filed provides an enabling disclosure of the presently claimed method of obtaining EPO by culturing mammalian cells in SF culture medium. For example, the specification as-filed provides a working example that discloses obtaining

EPO from a mammalian cell line that expressed EPO in "culture medium consisting of DMEM (Dulbecco's modified Eagle's medium), F12 medium, insulin, $NaHCO_3$, sugars, ethanolamine, pyruvate, and amino acids."

Contrary to the Examiner's assertion, the references Wang *et al.*, Yang. *et al.*, Schroder *et al.* and Lee *et al.* do not show that the state of the art is unpredictable for the production of recombinant proteins, specifically EPO, in cell culture using SF media. The SF medium of Schroeder *et al.* differs from the Examples of the present invention in that the SF medium comprises additives not contemplated in the presently claimed invention. These additives include vitamins, fetuin and *halo*-transferrin. (*See* Schroeder *et al.*, table 1, page 283.) More importantly, the reference teaches that the ordinary artisan can adapt a cell line to grow in SF medium and achieve production of the recombinant protein. Removal of protein components such as "fetuin and coating of the tissue culture dishes with 5 $\mu g/cm^2$ fibronectin did not interfere with the growth of any cell line." (*See* Schroeder *et al.*, 3.8 Protein-Free Medium Formulation, page 288.) "Only minor changes in the medium formulation were necessary for its use in the cultivation of anchorage-dependent and suspension cells. Adaptation of cells grown in the serum free formulation to a protein free medium was easy and straight forward." (*See* Schroeder *et al.*, 4. Conclusion, page 290.) As such, the reference clearly teaches that optimizing a media formulation to grow cells in SF medium is well within the skill of the ordinary artisan and would not require undue experimentation.

Further, the CHO-SFM2.1 SF medium of Wang *et al.* and Yang *et al.* was specifically developed for CHO cell lines producing EPO. The ingredients of the SF medium are not disclosed in the references; thus, the SF medium and methods cannot be

compared or contrasted to the methods and media claimed in the present invention. However, the references teach that although there may not be a single universal approach to optimize conditions for animal cell culture systems (*see e.g.* Wang *et al.* page 194, column 2, 1st paragraph), optimization is attainable with respect to cell growth, cell yield, and specific productivity. Even if different culture conditions have different effects because of the differences in various metabolites produced, this does not mean that the culture methods of the presently claimed invention are unpredictable. 35 U.S.C. § 112, first paragraph, only requires that the disclosure of the patent specification provide enough detail to allow the ordinary artisan to make and/or use the invention. Experimentation and optimization are permissible, provided it falls with the skill of the ordinary artisan, even if this requires a great deal of work. *See, e.g., In re Wands*, 858 F.2d at 737. Here, the specification has exemplified the cell growth and production of EPO using a SF medium.

The SF medium disclosed in Lee *et al.* uses a basal medium comprising IMDM, iron, copper, and zinc along with insulin, transferrin and ethanolamine in optimal concentrations. This media clearly differs from the presently claimed media. The reference of Lee *et al.* is directed to the development of SF medium for the production of EPO from CHO cells. The reference uses a statistical optimization approach, using a Plackett-Burman matrix, in the development of the SF medium. (*See* Lee *et al.* abstract.) The reference is a road map in how the ordinary artisan would go about optimizing the SF medium for the production of a recombinant protein in culture. "This statistical design technique enabled the development of the SF rapidly in a relatively small number of experiments." (*See* Lee *et al.* page 92, column 1, lines 21-23.) As such, the Lee *et al.*

reference provides further evidence that production of a recombinant protein in SF medium is enabled.

The Examiner further asserts that Applicants' disclosure "fails to disclose any other culture conditions (i.e. composition of nutrients used) for COS, BHK, Namalwa and Hela cells especially [in] context with the production of rEPO in serum free culture media as claimed." (OA at page 7.) The Examiner asserts that "[t]he state of the art clearly teaches that adaptation of cell lines to serum free conditions is [a] critical step in order to sustain viability and growth of recombinant cells." (OA at page 7.) It is clear from the combination of references cited by the Examiner that in order to produce rEPO from CHO cell lines, a variety of SF media can be used to successfully produce rEPO from the cells in culture. Here, the specification has exemplified the cell growth and production of EPO using a SF medium, that falls well within the scope of the claim. The Examiner has not presented any reason to doubt the objective truth of these experimental results; therefore, in view of the relevant case law, the present specification "must be taken as in compliance with the enabling requirement of the first paragraph of § 112."

3. The Experimentation is Routine

The Examiner has asserted that "the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue." (OA at page 8.) Applicants respectfully disagree.

A person of ordinary skill in the art could practice the present invention without undue experimentation, based on the guidance in the specification and the level of skill in the art. Undue experimentation does not mean "no" experimentation, only that it be reasonable. *See, e.g., In re Wands*, 858 F.2d at 737 ("The test is not merely quantitative,

since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed."). Contrary to the Examiner's assertion, it is clear from the combination of references cited that the state of the art is such that recombinant proteins can be successfully produced in cells grown in SF media without undue experimentation. The references teach a variety of SF media to produce rEPO from the cells in culture. The teaching in the art in conjunction with the Example provided in the specification indicate that a person of ordinary skill in the art at the time of filing would have possessed the knowledge and skills necessary to make and test the compositions of the present invention. Thus, any experimentation required to practice the present invention would have been reasonable, not undue.

In summary, claims 1-5, 7-13, 15-17 and 19-22 are fully enabled by the specification. Therefore, Applicants respectfully request reconsideration and withdrawal of this rejection.

II. Rejection Under 35 U.S.C. § 112, Second Paragraph

A. Claims 1-5, 7-13, 15-17, 19 and 20

The Examiner has rejected claims 1-5, 7-13, 15-17, 19 and 20 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regards as the invention. (OA at page 9.) More specifically, the Examiner asserts that claim 1 recites the broad limitation "an additive[ ] selected from the group consisting of NaHCO3, sugars, ethanolamine,

pyruvate, amino acids and mixtures thereof" while the claim also recites culture media "consisting of" which is the narrower statement of the range or limitation.

Applicants respectfully disagree with the application of this rejection. However, solely to advance prosecution, and not in acquiesce of any of the Examiner's assertions, claim 1 has been amended to read "culture medium consisting of DMEM (Dulbecco's modified Eagle's medium), F12 medium, insulin, $NaHCO_3$, sugars, ethanolamine, pyruvate, and amino acids." The amendment has not changed the scope of the claim and solely has been made to more clearly define the invention. Reconsideration and withdrawal of this rejection is respectfully requested.

III. Double Patenting

The Examiner rejected claims 1-5, 7-13, 15-17, 19 and 20 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 7-13 of U.S. Patent No. 6,777,205, for the same reasons of record as set forth in the Office Action mailed 12/29/05. (OA at page 10.) Applicants respectfully disagree with the Examiner's assertion. However, solely to advance prosecution, Applicants will submit a terminal disclaimer in accordance with 37 C.F.R. § 1.321(c) upon the notification by the Examiner of allowable subject matter.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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